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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/506,942	02/18/2000	Jean-Marc Balloul	032751-027	9626

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EXAMINER	
FOLEY, SHANON A	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 07/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/506,942	Applicant(s) BALLOUL ET AL.	
	Examiner Shanon Foley	Art Unit 1648	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 28 June 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *28 June 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *none*.
   Claim(s) objected to: *none*.
   Claim(s) rejected: *32,36,38,40,44,46,48,49,53-56,62,64,65,69,71-75,79 and 80*.
   Claim(s) withdrawn from consideration: *none*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See the attached correspondence.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). ____
13. ☐ Other: _____.

Shanon Foley
Primary Examiner
Art Unit: 1648

S.e.O.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 32, 36, 38, 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322), Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), and Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038), as further evidenced by Boursnell et al. (US 5,719,054) for reasons of record.

Applicant argues that none of the references teach ort suggest the pending claims. More specifically, applicant argues that Lowy et al. fail to demonstrate therapeutic protection against HPV-induced tumors. Applicant asserts that the anti-E7 antibodies generated by Lowy et al. do is not indicative of therapeutic efficacy. Applicant also asserts that the skilled artisan would not have had a reasonable expectation of success for producing the claimed invention with the recombinant MVA vector claimed. Applicant argues that the references would lead one skilled in the art to insert sequences of the early HPV peptides into the coding sequence of the late L2 polypeptide and that expression of multiple genes from different promoters from a single vaccinia vector could be difficult to achieve.

Since it is clearly evident from the combination teachings in the prior art cited that L1 and L2 papillomavirus polypeptides are prophylactic and that E6 and E7 papillomavirus

polypeptides are therapeutic from the prior art of record, it is prima facie obvious that a composition comprising these therapeutic and prophylactic elements would be therapeutic and prophylactic. One of ordinary skill in the art at the time the invention was made would have been motivated to combine the prophylactic papillomavirus polypeptides of Lowy et al. and Galloway with the therapeutic papillomavirus polypeptides of Galloway, Lowy et al., and Borysiewicz et al. to treat or prevent papillomavirus infection in a single composition. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing the claimed invention because L1 and L2 possess prophylactic properties (discussed by Lowy et al. and Galloway) and E6 and E7 possess ameliorative properties (discussed by Borysiewicz et al. and Galloway).

The combination of references clearly shows that expression of papillomavirus early polypeptides, E6 and E7, expressed from a vaccinia virus vector results in a therapeutic effect and that expression of papillomavirus late polypeptides, L1 and L2, expressed from a vaccinia vector, results in a prophylactic effect. Independent expression of four different papillomavirus polypeptides in a vaccinia virus vector is also expressly taught.

Therefore, it is maintained that one of ordinary skill in the art at the time the invention was made would have been motivated to express the HPV polypeptides of Lowy et al., Hagensee et al., Borysiewicz et al. and Galloway in the MVA vector of Meyer et al. under the control of different promoters, taught by Boursnell et al. to express the proteins from independent control elements in order to control transcription and subsequently, the amount of protein expressed in the cell. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of producing the construct claimed because Boursnell et al. teach

individual expression of different HPV polypeptides in a vaccinia vector and MVA of Meyer et al. is a vaccinia vector.

Regarding the teachings of Boursnell et al., applicant points to the legend of Figure 26, which illustrates a variety of options for the HPV coding sequences. Applicant summarizes the teachings of Boursnell et al., which discusses a variety of viral vectors that art suitable for simultaneously expressing one or more genes.

This is precisely the point of the Office. Boursnell et al. even exemplify separate expression of multiple papillomavirus genes from a vaccinia virus vector in Figure 26c.

Applicant argues that Boursnell et al. teaches that expressing multiple genes from independent promoters can be difficult to achieve and offers an opinion as to why the marker genes are eliminated. However, this opinion is not supported by the explicit examples and discussion provided by Boursnell et al.

Applicant's arguments have been fully considered, but are found unpersuasive. As pointed out in further teachings of Boursnell et al., difficulties expressing multiple genes from independent promoters is not a hindrance due to new methods briefly mentioned in the reference that eliminate the need for marker genes. Boursnell et al. also expressly illustrate the expression of four different papillomavirus genes from a vaccinia virus vector in Figure 26c. This figure provides a specific example that expressing multiple, un-fused HPV genes from a vaccinia viral vector is successfully achievable.

Applicant also discusses the lytic nature of vaccinia and the abortive nature of MVA and offers conjecture of whether these characteristics influence the immune response to infection. However, this speculation is unsupported by the prior art.

Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322), Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), and Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038), as further evidenced by Boursnell et al. (US 5,719,054), as applied to claims 32, 36, 38, 53 and 54 above, and further in view of Crook et al. (Cell. 1991; 67: 547-556) and Munger et al. (EMBO Journal. 1989; 8: 4099-4105) for reasons of record.

Applicant resubmits that in reference to the arguments presented for claim 32. However, these arguments are found unpersuasive and the rejection is maintained for reasons of record.

Claims 44, 46, 48, 55, 56, 62 and 64 rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322), Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), and Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038), as further evidenced by Boursnell et al. (US 5,719,054), as applied to claims 32, 36, 38, 53 and 54 above, and further in view of Bubenik et al. (International Journal of Oncology. 1996; 8: 477-481) for reasons of record.

Applicant argues that Bubenik et al. differs from the claimed invention because IL-2 is expressed from an MVA vector and is not separately administered. Applicant points to a teaching on pages 478 and 480 of Bubenik et al., which state that IL-2 was used to augment the protective efficacy of a vaccine comprising HPV E6 and E7.

With these citations, applicant has specifically identified a teaching of Bubenik et al. that provides specific motivation for using IL-2 in a papillomavirus composition, i.e. to augment the

immune response against HPV proteins. Applicant has also identified a teaching of Bubenik et al. that would have provided the ordinary artisan with a reasonable expectation of success for combining IL-2 in a papillomavirus vaccine composition, i.e. the inclusion of IL-2 increases the protective efficacy.

Applicant states that the method of Bubenik et al. requires multiple injections of IL-2 to induce an adjuvanting effect observed by Bubenik et al.

Applicant's arguments have been fully considered, but are found unpersuasive. As stated in the previous Office action, the amount of IL-2 administered to laboratory mice to achieve the adjuvanting effect observed by Bubenik et al. would be different from the amount required to achieve the same effect in humans. The amount required to achieve this effect is not a recited element of the claims. Moreover, it is conventional in the vaccine art to optimize doses, i.e. the amount of MVA vector required to be administered to achieve an efficacious concentration. Differences in concentrations will not support the patentability of subject matter unless there is some evidence indicating that the required concentration is critical to the invention. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Applicant also states that the art recognizes that expressing multiple genes in a single vaccinia vector may be problematic. However, this statement is explicitly unsupported in column 3, lines 29-35, column 8, lines 24-37 and Figure 26c of Boursnell et al.

Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322), Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038), as further evidenced by

Boursnell et al. (US 5,719,054), and Bubenik et al. (International Journal of Oncology. 1996; 8: 477-481) as applied to claims 32, 36, 38, 44, 46, 48, 53-56, 62 and 64 above, and further in view of Crook et al. (Cell. 1991; 67: 547-556) and Munger et al. (EMBO Journal. 1989; 8: 4099-4105) for reasons of record.

Applicant reiterates the arguments presented for claim 48, from which claim 49 depends.

These arguments are found unpersuasive and the rejection is maintained for reasons of record. The rebuttal for these arguments is repeated herein.

Claims 65, 69, 71, 72, 74, 79 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038) and Bubenik et al. (International Journal of Oncology. 1996; 8: 477-481), as further evidenced by Boursnell et al. (US 5,719,054) for reasons of record.

Applicant argues that Borysiewicz et al. fail to disclose or suggest the inclusion of an immunostimulatory polypeptide or independent expression of each gene. Applicant also argues that Bubenik et al. requires repeated administrations of IL-2, Boursnell et al. caution expression of more than two independent genes in a vaccinia vector, and Meyer et al. discuss differences between MVA and wild-type vaccinia.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Borysiewicz et al. is not required to teach an immunostimulatory polypeptide or independent expression of multiple genes since Bubenik et al., Boursnell et al. and Meyer et al. not only teach the elements missing from the teachings of Borysiewicz et al., but they also provide specific motivations for combining the elements taught with other elements in the prior art with a reasonable expectation of success for the ordinary artisan once combined.

Regarding the quantity of IL-2 administered to mice by Bubenik et al. to induce an augmenting immune response, Bubenik et al. explicitly teach that IL-2 induces an adjuvanting effect when administered with a composition against papillomavirus. The amount of IL-2 required to be expressed from the instant vector is not a required element. Further, the amount of expression from the instant vector and the amount of vector administered would be of routine design by one of ordinary skill.

As pointed out in further teachings of Boursnell et al., difficulties expressing multiple genes from independent promoters is not a hindrance due to new methods briefly mentioned in the reference that eliminate the need for marker genes. Boursnell et al. also expressly illustrate the expression of four different papillomavirus genes from a vaccinia virus vector in Figure 26c.

Finally, Meyer et al. teach six major deletion sites in the wild-type vaccinia Ankara strain attenuate virus pathogenicity to MVA that are not essential to viral replication and, see the abstract and the results section on page 1032-1034. In addition, Meyer et al. teach that the insertion of the K1L gene of the MVA vaccinia strain leads to increased host range and suggests this as a selection system for recombinant viruses expressing foreign genes, see page 1037.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate IL-2 of Bubenik et al. into the MVA vaccinia vector of Meyer et al.

expressing E6 and E7 proteins of Borysiewicz et al. to augment the immune response to the papillomavirus polypeptides. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for expressing IL-2 in the MVA vaccinia vector of Meyer et al. because Borysiewicz et al. teach expressing papillomavirus polypeptide genes in a vaccinia vector and Meyer et al. use MVA vaccinia virus that allows multiple insertion sites for heterologous inserts. Therefore, one of ordinary skill would have been able to express various papillomavirus polypeptides as well as IL-2 in an MVA vector with a reasonable expectation of success. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claim 75 is rejected under 35 U.S.C. 103(a) as being unpatentable over Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038) and Bubenik et al. (International Journal of Oncology. 1996; 8: 477-481) as applied to claims 65, 69, 71, 72, 74, 79 and 80 above, and further in view of Crook et al. (Cell. 1991; 67: 547-556) and Munger et al. (EMBO Journal. 1989; 8: 4099-4105), as further evidenced by Boursnell et al. (US 5,719,054) for reasons of record.

Applicant refers to the comments of claim 65 to argue the rejection of claim 75.

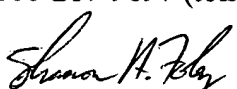
These arguments were considered above, but were found unpersuasive. The rebuttal for these arguments is resubmitted herein.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (571) 272-0898. The examiner can normally be reached on M-F 6:00 AM - 2:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Shanon Foley
Primary Examiner
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